CLAIMS

What is claimed is:

1. A composition for the sustained release of biologically active, non-aggregated erythropoietin from a polymeric matrix, comprising:
   a) a biodegradable polymer; and
   b) particles of biologically active, aggregation-stabilized erythropoietin, wherein said particles include erythropoietin in contact with a salting-out salt, and wherein said erythropoietin particles are dispersed within the polymeric matrix.

2. A sustained release composition of Claim 1 wherein the salting-out salt comprises a salt containing a cation selected from the group consisting of Mg^{+2}, Li^{+}, Na^{+}, K^{+}, NH_4^{+} and combinations thereof.

3. A sustained release composition of Claim 1 wherein the salting-out salt comprises a salt containing an anion selected from the group consisting of SO_4^{-2}, HPO_4^{-2}, acetate, citrate, tartrate, Cl^{-}, NO_3^{-}, ClO_3^{-}, I^{-}, ClO_4^{-}, SCN^{-} and combinations thereof.

4. A sustained release composition of Claim 1 wherein the salting-out salt is ammonium sulfate.

5. A sustained release composition of Claim 1 wherein the biodegradable polymer is selected from the group consisting of poly(lactides), poly(glycolides), poly(lactide-co-glycolides), poly(lactic acid)s, poly(glycolic acid)s, poly(lactic acid-co-glycolic acid)s, polycaprolactone, polycarbonates, polyesteramides, polyanhydrides, poly(amino acids), polyorthoesters, polycyanoacrylates, poly(p-dioxanone), poly(alkylene oxalate)s, biodegradable polyurethanes, blends and copolymers thereof.

6. A sustained release composition of Claim 5 wherein said polymer comprises poly(lactide-co-glycolide).

7. A sustained release composition of Claim 1 further comprising a metal cation component, wherein the metal cation component is not contained in said erythropoietin particles, and wherein the metal cation component is dispersed within the biodegradable polymer to modulate the release of erythropoietin from the polymeric matrix.

8. A sustained release composition of Claim 7 wherein the metal cation component is selected from the group consisting of magnesium hydroxide, magnesium carbonate, calcium carbonate, zinc carbonate, magnesium acetate, zinc acetate, magnesium sulfate, zinc sulfate, magnesium chloride, zinc chloride, zinc citrate, magnesium citrate and combinations thereof.

9. A method for forming a composition for the sustained release of biologically active erythropoietin from a polymeric matrix, comprising the steps of:

a) dissolving a biodegradable polymer in a polymer solvent to form a polymer solution;

b) dispersing particles of biologically active, aggregation-stabilized erythropoietin in the polymer solution, wherein said particles include erythropoietin in contact with a salting-out salt; and

c) solidifying the polymer to form a polymeric matrix containing a dispersion of said erythropoietin particles.

10. A method of Claim 9 wherein the salting-out salt comprises a salt containing an anion selected from the group consisting of SO_4^{-2}, HPO_4^{-2}, acetate, citrate, tartrate, Cl^-, NO_3^-, ClO_3^-, I^-, ClO_4^-, SCN^- and combinations thereof.

11. A method of Claim 9 wherein the salting-out salt comprises a salt containing a cation selected from the group consisting Mg^{+2}, Li^{+}, Na^{+}, K^{+}, NH_4^{+} and combinations thereof.

12. A method of Claim 9 wherein the salting-out salt is ammonium sulfate.

13. The method of Claim 9 further comprising the step of dispersing a metal cation component within the polymer solution, wherein the metal cation component is not contained in the erythropoietin particles.

14. A method of Claim 13 wherein the metal cation component is selected from the group consisting of magnesium hydroxide, magnesium carbonate, calcium carbonate, zinc carbonate, magnesium acetate, zinc acetate, magnesium sulfate, zinc sulfate, magnesium chloride, zinc chloride, zinc citrate, magnesium citrate and combinations thereof.

15. A method for forming microparticles for the sustained release of biologically active, non-aggregated erythropoietin, comprising the steps of:

a) mixing biologically active erythropoietin with a salting-out salt and with a buffer, wherein said buffer has a pH between about 4 and about 8, to form an aggregation-stabilizing mixture; and

b) lyophilizing said mixture to form biologically active, aggregation-stabilized erythropoietin;

c) dispersing particles of biologically active, aggregation-stabilized erythropoietin in a polymer solution to form a dispersion;

d) freezing droplets of the dispersion to form microparticles; and

e) contacting the microparticles with a liquid non-solvent, which is miscible with the polymer solvent, whereby the polymer solvent is extracted from the microparticles, thereby forming microparticles for the sustained release of biologically active, non-aggregated erythropoietin.

16. A method for providing a therapeutically effective blood level of biologically active, non-aggregated erythropoietin in a subject for a sustained period, comprising administering to the subject a dose of the sustained release composition of Claim 1.

17. A method of Claim 16 wherein the salting-out salt comprises a salt containing a cation selected from the group consisting of Mg^{+2}, Li^{+}, Na^{+}, K^{+}, NH_4^{+} and combinations thereof.

18. A method of Claim 16 wherein the salting-out salt comprises a salt containing an anion selected from the group consisting of SO_4^{-2}, HPO_4^{-2}, acetate, citrate, tartrate, Cl^{-}, NO_3^{-}, ClO_3^{-}, I^{-}, ClO_4^{-}, SCN^{-} and combinations thereof.